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Tardive dyskinesia is associated with impaired retrieval from long-term memory: the Curaçao Extrapyramidal syndromes study: IV

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Abstract

Tardive dyskinesia may be associated with cognitive dysfunction. It is not clear whether this dysfunction occurs in the form of a global or specific cognitive deficit. A cross-sectional study was conducted in a well-defined catchment area (Curaçao, The Netherlands Antilles). All schizophrenic inpatients who had been taking neuroleptic medication for at least 3 months and who were younger than 65 years were included ($n=53$). Tardive dyskinesia was assessed with the Abnormal Involuntary Movement Scale. The neuropsychological assessment comprised tests of memory, executive function, and speed of information processing. Of the six cognitive measures, only delayed recall was significantly associated with orofacial dyskinesia. Limb–truncal dyskinesia was not associated with any of the cognitive measures. The pattern of memory impairment is consistent with there being a frontal-subcortical disturbance in orofacial dyskinesia. The results underscore the importance of using specific cognitive test procedures in the search for the cognitive correlates of dyskinesia.

Keywords: Memory; Neuropsychology; Schizophrenia; Tardive dyskinesia

1. Introduction

Tardive dyskinesia is one of the most important iatrogenic disorders in psychiatry because of its frequent occurrence and possible irreversibility. Identifying risk factors for dyskinesia is clinically relevant for prevention of the disorder. A putative risk factor is cognitive dysfunction (Paulsen et al., 1994; Waddington and Youssef, 1996). In a review, Waddington (1995) concluded that despite a range of potential methodological confounds, cognitive dysfunction is a robust clinical correlate of dyskinesia in schizophrenia. In particular, the orofacial form of dyskinesia appears to be associated with cognitive impairment (Brown et al., 1992; Waddington et al., 1993; Waddington and Youssef, 1986). It is not clear whether this dysfunction occurs in the form of a global or specific cognitive deficit, such as frontal executive functions of

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memory. This is due to the use of rather global cognitive assessment methods, such as the Mini Mental State Examination (e.g., Brown and White, 1992; Davis et al., 1992), or summary scores derived from a number of tests (e.g., Wade et al., 1989). The goal of the present study was to specify the association between cognitive dysfunctions and orofacial and/or limb–truncal dyskinesia. The study was part of a large longitudinal study on the prevalence and incidence of extrapyramidal syndromes in Curaçao (Van Harten et al., 1996, 1997).

2. Methods

2.1. Subjects

The study was performed at the Dr D.R. Capriles Hospital on Curaçao, the main island of the Netherlands Antilles. The patients were selected from a sample described in detail elsewhere (Van Harten et al., 1996). Patients were eligible for the study if they met the following criteria: (i) informed consent; (ii) diagnosed with schizophrenia according to DSM-III-R (American Psychiatric Association, 1987); (iii) no organic disorders that could cause movement disorders; (iv) a history of neuroleptic use for at least 3 months; and (v) younger than 65 years. The latter inclusion criterion was used to avoid the confounding effects of the ageing process. A total of 64 patients fulfilled the inclusion criteria. Eleven patients (17.2%) could not be assessed, because of severe agitation (7), lack of co-operation (3), or sensory deficits (1). The group consisted of 47 male and 6 female subjects. The mean age was 49.2 years (SD = 8.6). Mean age at first admission was 22.0 years (SD = 6.3); mean total duration of hospitalisation was 16.0 years (SD = 10.3). Most of the patients (75.5%) had a low level of education (primary school or vocational training for 12–16 year olds), 18.8% of the patients had a medium level of education (secondary education or vocational training for 16–18 year olds), and 5.7% of the patients had a high level of education (higher education or vocational training for 18+). The level of education was relatively low compared with that of other study samples described in the literature, and so this variable was incorporated in the regression analyses to adjust for education effects. All subjects took neuroleptic medication at the time of the assessment (mean dose in chlorpromazine equivalents 732; SD = 638); 50.9% of the patients used anticholinergics, 7.5% used antidepressants, 9.4% used lithium, and 35.3% used benzodiazepines. Because of possible effects on cognitive performance, the current use of psychoactive medication was controlled for in the analysis.

2.2. Assessments

The neuropsychological assessment was directed at the following cognitive domains: recall from short-term and long-term memory and recognition, general speed of information processing, and frontal executive functions. The Picture Learning Test was used to assess recall and recognition. The test is based upon the Auditory Verbal Learning test (Brand and Jolles, 1985). It yields scores for immediate recall, delayed recall (after 20 min), and delayed recognition. The Letter Digit Substitution Test was used to assess speed of general information processing. This test is a modified version of the Symbol Digit Modalities Test (Smith, 1968). The Stroop Colour–Word Test (Stroop, 1935) was used to assess frontal executive functioning. This test involves three cards, which display colour names, coloured patches, and colour names printed in incongruously coloured ink, respectively. Card I involves general information processing, whereas performance on card III reflects frontal executive functioning.

The assessment of tardive dyskinesia has been described in detail elsewhere (Van Harten et al., 1996). In short, tardive dyskinesia was assessed with the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976), with case definition according to the criteria of Schooler and Kane (1982). The prevalence of tardive dyskinesia in the current patient group has been assessed approximately each year since 1992. In the current study, the 1996 and 1997 measurements were used. Presence of tardive dyskinesia was defined as a diagnosis of dyskinesia on both occasions.

Orofacial and limb–truncal dyskinesia were defined inclusively, meaning that a patient could have either orofacial or limb–truncal dyskinesia, or both. The severity of orofacial and limb–truncal dyskinesia was computed by summing the scores for the first four items of the AIMS and for the fifth to seventh items, respectively.

The presence of parkinsonism was assessed with the Unified Parkinson Disease Rating Scale (Martínez-Martín et al., 1994), and cases were defined as described previously (Van Harten et al., 1996).

2.3. Data analysis

All analyses were conducted using the SPSS statistical package for Macintosh (version 6.1). Multiple logistic regression analyses and multiple linear regression analyses were performed to analyse the relationship between each cognitive measure and orofacial or limb–truncal dyskinesia, adjusted for age, sex, level of education, current dose of neuroleptics, parkinsonism, and current use of anticholinergics, antidepressants, lithium or benzodiazepines. The resulting regression coefficients and odds ratios reflect the adjusted correlations between specific cognitive dysfunctions and orofacial or limb–truncal dyskinesia.

3. Results

The prevalence of tardive dyskinesia was 41.5% (22 patients). Of the 22 patients, 10 had both orofacial and limb–truncal dyskinesia, 9 had orofacial dyskinesia only, and 3 had limb–truncal dyskinesia only. Parkinsonism was present in 28.3% (15) of the patients.

The results of the logistic and linear regression analyses for each of the cognitive variables are shown in Table 1. After adjustment for confounders, the delayed recall of the Picture Learning Task was significantly associated with both the occurrence and the severity of orofacial dyskinesia, with a poorer performance being associated with a higher risk and a greater severity of orofacial dyskinesia (OR = 1.55, 95% CI = 1.05 –2.27; B = 0.66, 95% CI = 0.01–1.31). Without adjustment for confounders, the odds ratio for delayed recall was 1.36 (95% CI = 1.08–1.71), which was significant (Wald $\chi^2 = 6.74$, df = 1, $p < 0.01$). The other cognitive variables were not related to the occurrence or severity of orofacial dyskinesia, and none of the cognitive variables were associated with limb–truncal dyskinesia.

4. Discussion

This study shows that orofacial dyskinesia is associated with a specific cognitive dysfunction,

Table 1
Relation of specific cognitive variables to the occurrence and severity of orofacial and limb–truncal dyskinesia ($n = 53$)

Cognitive variable[a]	Logistic regression		Linear regression	
	Orofacial dyskinesia adjusted OR (95% CI)	Limb–truncal dyskinesia adjusted OR (95% CI)	Orofacial dyskinesia B (95% CI)	Limb–truncal dyskinesia B (95% CI)
Picture Learning Test				
Immediate recall	1.11 (0.95–1.30)	1.04 (0.90–1.22)	0.02 (−0.34–0.37)	−0.02 (−0.23–0.19)
Delayed recall	1.55[b] (1.05–2.27)	1.26 (0.91–1.76)	0.66[c] (0.01–1.31)	0.12 (−0.30–0.54)
Recognition	1.22 (0.62–2.41)	1.71 (0.51–5.72)	0.28 (−1.60–2.17)	−0.11 (−1.19–0.97)
Letter Digit Substitution Test	1.07 (0.93–1.22)	1.01 (0.87–1.18)	0.05 (−0.36–0.26)	−0.04 (−0.22–0.15)
Stroop Colour Word Test card I	1.00 (0.92–1.09)	1.07 (0.94–1.21)	−0.03 (−0.26–0.19)	−0.05 (−0.19–0.08)
Stroop Colour Word Test card III	1.01 (0.98–1.04)	1.01 (0.98–1.05)	0.03 (−0.03–0.09)	−0.01 (−0.5–0.02)

[a] All cognitive variables were recoded such that higher scores meant worse performance.
[b] Wald $\chi^2 = 4.98$; df = 1; $p < 0.03$.
[c] $T = -2.05$; df = 35; $p < 0.05$.

namely, impaired active retrieval from long-term memory. Our study specifies the relationship between cognitive dysfunction in patients with tardive dyskinesia, which has been reported previously (e.g., Paulsen et al., 1994; Waddington and Youssef, 1996). Our results are consistent with an early study that also reported the specific association with delayed recall (Thomas and McGuire, 1986), although this study did not include a measure of recognition. Further, Myslobodsky et al. (1985) reported a significant association between orofacial tardive dyskinesia and picture recall. The validity of our findings is supported by the fact that (i) the analysis was adjusted for factors which may influence cognitive performance, including demographic variables, parkinsonism, as well as use of psychoactive medication, and (ii) dyskinesia was assessed at two points in time, which improves the validity of the diagnosis.

4.1. Risk factor or state marker

Due to the cross-sectional design of the study, we could not determine whether cognitive dysfunction is a risk factor for the development of orofacial dyskinesia or a state marker of the disorder (Waddington et al., 1993). There is some evidence from prospective studies that patients with schizophrenia associated with cognitive deterioration have an increased risk of dyskinesia. In one study, patients with chronic schizophrenia who had developed orofacial dyskinesia by the 5 year follow-up were not distinguishable from non-dyskinetic patients at the initial assessment (Waddington and Youssef, 1996). However, the emergence of orofacial dyskinesia was associated with concurrent deterioration of cognitive functions. In another prospective study, poor cognitive performance was associated with greater likelihood of subsequent emergence of tardive dyskinesia in a heterogeneous outpatient population (Wegner et al., 1985). Our results suggest that this risk factor can be specified as an impairment of delayed recall. The results further indicate that this risk factor is independent of the effect of antipsychotic medication, because the association between impaired memory and tardive dyskinesia was not affected by current exposure to antipsychotic medication. This is in line with the suggestion that there might be two factors which independently act to increase the risk of tardive dyskinesia (Van Os et al., 1997). One factor is exogenous (antipsychotic medication) and the other involves illness-related aspects, notably cognitive deterioration, which most likely reflects disturbed brain function.

4.2. Pathophysiological implications

Although an impairment of memory could suggest temporal lobe/hippocampal involvement (Tranel and Damasio, 1995), the association with active recall but not recognition is more in line with the pattern of memory impairment in patients with basal ganglia pathology, such as Huntington's and Parkinson's disease (Brandt and Rich, 1995). This suggests that similar structures underlie the cognitive impairment in orofacial dyskinesia. A detailed model of basal ganglia function proposes that five circuits subserve different areas of the prefrontal cortex (Alexander et al., 1986). These frontal-subcortical circuits, and especially those that subserve cognitive function, may be involved in schizophrenia (Pantelis and Brewer, 1996). More severe disturbance of these circuits, as evidenced by impaired active recall, may increase the risk for orofacial dyskinesia. This hypothesis is in accordance with a recent study, in which orofacial dyskinesia was found to be associated with poor performance on a test of frontal functioning, the Wisconsin Card Sorting Test (Waddington et al., 1995). Surprisingly, in the present study there was no association between orofacial dyskinesia and another putative measure of frontal lobe functioning, performance on the Stroop Colour–Word Test card III. This may indicate that this task involves frontal-subcortical circuits other than those affected in orofacial dyskinesia. The topographical specificity of the association, i.e., with orofacial as opposed to limb–truncal dyskinesia, provides further evidence that the two forms involve different pathophysiological mechanisms. The frontal-subcortical disturbance may well be specific to orofacial dyskinesia. Limb–truncal dyskinesia may be associated with treatment-related factors, such as current medication (Bergen et al., 1992; Glazer et al., 1988; Gureje, 1989), but this could not be

confirmed in another study (Waddington et al., 1987).

4.3. Limitations

The relatively low mean level of education in the study sample may limit extrapolation of the results to more highly educated patients. However, the effect of level of education was adjusted for in the statistical analysis.

The fact that we studied an African-Caribbean population might limit the extent to which the results can be generalised to other populations. However, the main epidemiological characteristics of the sample, such as admittance rate, percentage of schizophrenic patients, and mean current dosage of neuroleptic medication, are similar to those of other studies (Van Harten et al., 1996).

The selected sample represented about 12% of the estimated total population of schizophrenic patients on the island, and consisted of (i) patients who were in hospital, and who may therefore have had a more severe form of psychosis, and (ii) patients younger than 65 years. Whether the result can be generalised to the total population of patients with schizophrenia is not clear. However, there is no a priori reason to assume that the relation between tardive dyskinesia and cognitive dysfunction will be different in less severely ill patients.

5. Conclusion

The present study shows that orofacial dyskinesia is associated with a specific impairment of retrieval. The pattern of memory impairment is consistent with there being a frontal-subcortical disturbance in orofacial dyskinesia. The results underscore the importance of using specific cognitive test procedures in the search for the cognitive correlates of dyskinesia.

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